Jikeikai Med J 2006 ; 53 : 15-21

Clinical Study of Skin Toxicity Associated with Gefitinib in Advanced Non-Small Cell Lung Cancer : Is Skin Toxicity A Predictor of Survival ?

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ABSTRACT

Gefitinib is a new epidermal growth factor receptor tyrosine kinase inhibitor for the treatment of non-small cell lung cancer (NSCLC). The main adverse effects of this drug are diarrhea and skin toxicity. In recent studies, patients with skin toxicity have shown a good response to gefitinib. In this study, we reviewed 43 patients with advanced NSCLC treated with gefitinib from August 2002 through July 2004 at The Jikei University Hospital in Tokyo. Two patients had a complete response, and 3 patients had a partial response. The response rate was 11.6%. Skin toxicity developed in 23 patients (53.5%) during treatment with gefitinib. Contrary to our expectations, we did not find a significant difference in survival between patients with skin toxicity and those without ($p=0.8588$). However, this failure to find a difference in survival might have been influenced by our study being retrospective with a small number of patients and a relatively low response rate. Further research is needed regarding the mechanism of skin toxicity in patients with NSCLC treated with gefitinib. (Jikeikai Med J 2006 ; 53 : 15-21)

Key words : non-small cell lung cancer, gefitinib, skin toxicity, survival

INTRODUCTION

Lung cancer has become the most common cause of cancer-related death in many countries. Although platinum-based chemotherapy has become the standard treatment for advanced non-small cell lung cancer (NSCLC), the 5-year survival rate with chemotherapy alone is nearly 0%[1]. Therefore, new anticancer agents are needed. With recent developments in molecular biology, several biomarkers relevant to neoplasms have been discovered, one of which is epidermal growth factor receptor (EGFR).

EGFR is a member of the ErbB family of transmembrane tyrosine kinase receptors which includes ErbB1 (or HER-1, or EGFR), ErbB2 (or HER-2/neu), ErbB3 (or HER-3), and ErbB4 (or HER-4)[2,3]. The expression of EGFR is commonly observed in normal epithelial tissues and is enhanced in some solid tumors[2,3]. In several studies of NSCLC, EGFR was overexpressed in more than half the cases[2,3]. These studies have also identified EGFR expression as a negative prognostic factor in patients with resected early NSCLC[2,3].

Gefitinib (Iressa, Astra Zeneca, Wilmington, DE, USA) is an orally active, selective EGFR tyrosine kinase inhibitor (EGFR-TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and other host-dependent processes promoting cancer growth[4]. Two large-scale, multicenter, randomized phase II trials, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 studies, showed that gefitinib

Received for publication, November 29, 2005

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has substantial effects even when used alone as a salvage treatment in patients previously treated with conventional chemotherapy[5,6].

IDEAL 1 was conducted mainly in Japan and Europe. Patients who had previously been treated with one or two chemotherapy regimens including a platinum compound were randomly assigned to receive 250 or 500 mg of gefitinib per day. The response rate approached 20% in both arms, and the rate of symptom improvement was approximately 40%. The higher dose of gefitinib (500 mg) was more toxic and more often induced an acne-like rash and diarrhea. Dry skin, acneiform skin, and pruritis were observed in 10.6%, 30.8% and 45.5% of patients, respectively. Thereafter, gefitinib was well tolerated at a dose of 250 mg per day.

Subset analysis of the IDEAL 1 study showed that ethnicity played an important role in the response to gefitinib. The response rate was signficantly higher in Japanese patients (27.5%) than in non-Japanese patients (10.4%). Furthermore, multivariate analysis also showed significantly higher response rates in female patients and patients with adenocarcinoma.

The main adverse effects of gefitinib are diarrhea, skin toxicity, and liver dysfunction. Diarrhea was the dose-limiting toxicity in phase I trials. Skin toxicity has been documented in several case reports[7-9]. Interstitial lung disease has been also observed in patients receiving gefitinib; in Japan, interstitial lung disease has developed in 5.81% of patients, with approximately a third of cases being fatal[10].

Some recent reports suggest that skin toxicity is related to prognosis in such patients[11,12]. Ezra et al. have shown that in a series of 52 patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with gefitinib a performance status (PS) and the development of skin toxicity were strong predictors of response, progression, and survival[11]. Mohamed et al have reported that in a series of 199 patients who had NSCLC treated with gefitinib, median survival in patients with rash of any grade (10.8 months) was longer than that in patients without rash (4.0 months)[12].

Therefore, the aim of this study was to examine the relation between skin toxicity and survival in patients with NSCLC treated with gefitinib at our hospital.

Patients and Methods

We reviewed patients with NSCLC treated with gefitinib from August 2002 through July 2004 at The Jikei University Hospital in Tokyo. All patients were treated with a single regimen of gefitinib, 250 mg orally per day. Data collected included sex, age, histologic type of lung cancer, clinical stage, smoking history, and the presence of skin toxicity. We could not confirm patients' PS because the clinical records were incomplete. The response rate and the overall survival rate were calculated. Responses were defined according to the Response Evaluation Criteria in Solid Tumors criteria[13], and the severity of all adverse events related to gefitinib was assessed with the National Cancer Institute-Common Toxicity Criteria (NCT-CTC) version 2.0 grading system[14].

Survival curves were estimated with the Kaplan-Meier method and compared between patients with skin toxicity and those without by means of the log-rank test. Differences with P values less than 0.05 were considered significant. Comparisons of background characteristics between groups were performed with the unpaired t-test. All analyses were performed with Stat View Version 5.0 for Macintosh (SAS Institute Inc., Cary, NC, USA).

Results

From August 2002 through July 2004 gefitinib was administered to 50 patients with NSCLC at The Jikei University Hospital in Tokyo. Seven patients were excluded from analysis because of insufficient data (4 patients), long-term drug cessation (2 patients), or treatment withdrawal due to vomiting (1 patient). The remaining 43 patients were included in this analysis. The baseline characteristics (Table 1) did not differ significantly between patients with and without skin toxicity.

Two patients showed a complete response (CR), and 3 patients showed a partial response (PR) for a

Table 1. Patient characteristics

Characteristics	No. of patients (%)			p-value (t test)
	skin toxicity	no skin toxicity	All patients	
Patients	23	20	43	
Age (years)				
Median	59	60	60	$p=0.8710$
Range	36-80	36-78	36-80	
Sex				
Male	17	13	30	$p=0.5369$
Female	6	7	13	
Histologic subtype				
Adenocarcinoma	18	17	35	$p=0.5818$
Squamous cell carcinoma	4	2	6	
Large cell carcinoma	1	1	2	
Stage				
I B	0	1	1	$p=0.3269$
IIIB	3	3	6	
IV	20	16	36	
Smoking				
Never	8	9	17	$p=0.3360$
Ever	15	11	26	
Prior chemotherapy regimens				
0	8	7	15	$p=0.8417$
1	11	10	21	
2	4	3	7	

Table 2. Type of skin toxicity

Skin toxicity	Patient No. (%)
Rash	17 (39.5%)
Dry skin	7 (16.3%)
Paronychia	4 (9.3%)
Stomatitis	2 (4.7%)

Table 3. Incidence of drug related skin toxicity by NCI-CTC grade

	NCI-CTC				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Skin toxicity	12	10	1	0	23

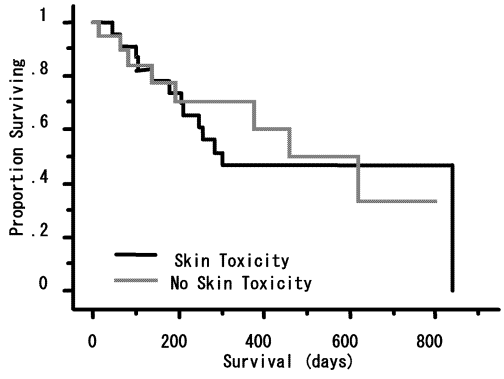

Fig. 1. Kaplan-Meier plot of overall survival for patients with and without skin toxicity

response rate (CR+PR) of 11.6%. Stable disease was achieved in 23 patients, and progressive disease (PD) was observed in 15 patients.

Of the 43 patients, 23 (53.5%) had skin toxicity during treatment with gefitinib. Rash, including acneiform eruption, erythema, and flare, was the most frequent skin toxicity (17 patients). Other skin toxicities included dry skin, paronychia, and stomatitis (Table 2). Skin toxicities were generally mild, with most being grade 1 to 2 (Table 3). Grade 3 skin toxicity was observed in only 1 patient.

Overall survival did not differ significantly between patients with and without skin toxicity ($p=0.8588$, log-rank test ; Fig. 1). Survival was slightly but not significantly longer in nonsmoking patients

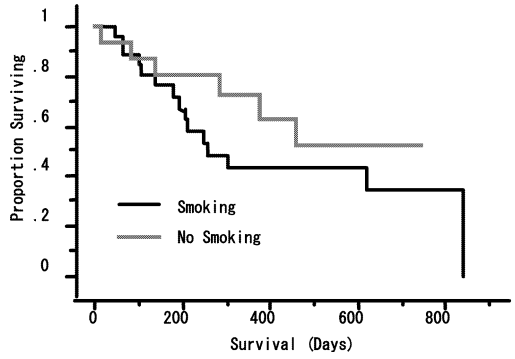

Fig. 2. Kaplan–Meier plot of overall survival for patients with and without smoking

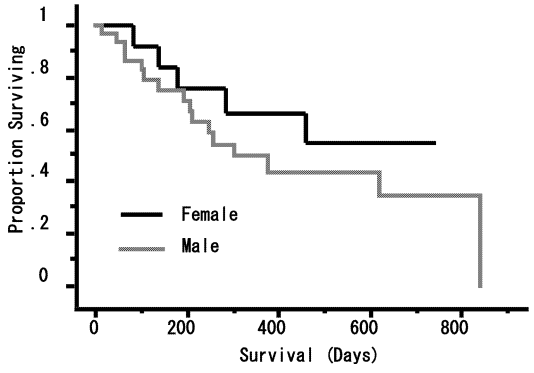

Fig. 3. Kaplan–Meier plot of overall survival for sex

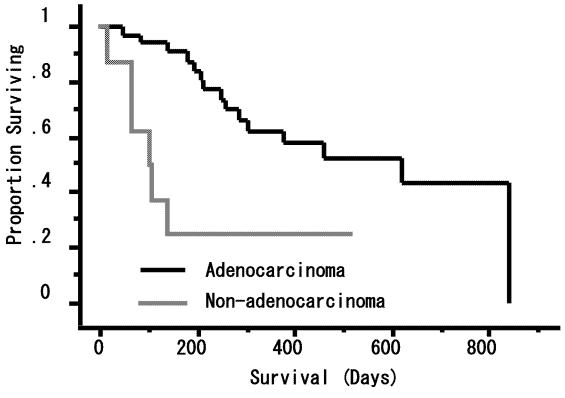

Fig. 4. Kaplan–Meier plot of overall survival for histologic type

(Fig. 2, $p=0.2816$) and in female patients (Fig. 3, $p=0.3419$). However, histologic type had a significant effect on survival; patients with adenocarcinoma survived longer than did patients with other types of lung cancer (Fig. 4, $p=0.0018$).

DISCUSSION

Gefitinib is a new agent for the treatment of advanced NSCLC. It is the first drug to be categorized as an EGFR-TKI. The safety and tolerability of gefitinib have been confirmed by four open-label, multicenter, phase I dose-escalation studies[4,15–17]. The major adverse effects were diarrhea, rash, elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT), and nausea but were mild and tolerable. In these studies, the rate of rash was 32% to 65%.

Two large-scale, multicenter, randomized phase II studies (IDEAL 1 and 2) have demonstrated the clinically significant antitumor activity of gefitinib monotherapy in patients with advanced NSCLC who had previously received platinum-based chemotherapy[3,4]. The response rate for gefitinib (250 mg per day) in the IDEAL 1 and 2 trials was 18.4% and 11.8%, respectively. These studies have also shown that gefitinib monotherapy significantly improves disease-related symptoms and quality of life.

In IDEAL 1[5], 210 patients with advanced NSCLC who had previously been treated with one or two chemotherapy regimens (at least one containing platinum) were randomly assigned to receive either 250 mg or 500 mg of gefitinib once daily. Efficacy was similar with either 250 mg or 500 mg per day. Adverse effects with both doses were generally mild (grade 1 or 2) and consisted mainly of skin reactions and diarrhea. Drug-related toxicities were more frequent with the higher dose. Skin toxicities, including

Table 4. The summary of phase I study about skin toxicity

Author	Total patients	Patients with skin rash	Grade 1–2	Grade ≥3
Baselga[15]	88	57 (65%)	55	2
Herbst[16]	69	38 (55%)	32	6
Ranson[4]	64	34 (53%)	33	1
Nakagawa[17]	31	10 (32.3%)	10	0

rash, pruritus, dry skin, and acne, were generally mild. Patients with rash also frequently reported other skin-related symptoms, including acne (10.6%), pruritus (45.5%), and dry skin (30.8%). In most patients, these skin disorders resolved during treatment or temporary therapy interruption or following treatment cessation. Two patients receiving 500 mg per day withdrew from the trial because of skin disorders after 7 and 10 days of treatment (one with grade 3 rash and one with grade 1 rash). Concurrent rash and diarrhea were seen in 15.5% and 22.5% of patients receiving gefitinib at 250 and 500 mg/day, respectively.

In IDEAL 2[6], 216 received either 250 mg or 500 mg gefitinib per day. Skin toxicity, described variably as rash, acne, dry skin, or pruritus, was observed in 62% of patients receiving 250 mg of gefitinib and in 75% of those receiving 500 mg. The rash appeared on the face, neck, and trunk and commonly faded or improved despite treatment being continued. Rash occurred during the first treatment cycle in 82% of patients. Skin toxicity was observed in all 22 patients with PR and in 65% of patients without a PR. Skin toxicity was documented in 86% of patients with symptom improvement and in 58% of those whose symptoms did not improve.

In the review, skin toxicity due to EGFR inhibitors have included acneiform eruption, xerosis, nail change, hair change, telangiectasia, and hyperpigmentation[18]. The mechanism by which EGFR inhibition leads to these adverse skin events is largely unknown.

Takano et al. have reported a retrospective analysis of 112 patients with advanced NSCLC who received gefitinib monotherapy[19]. They observed an association between efficacy and toxicity. Patients who had rash or elevated AST/ALT levels tended to exhibit a treatment response, and skin rash, diarrhea, and elevated AST/ALT levels were significant indicators of survival.

Erlotinib is a highly specific EGFR-TKI similar to gefitinib. In a phase II study of 57 patients by Soler et al.[20], a continuous daily dose of 150 mg of erlotinib produced rash in 75% of patients and diarrhea in 56% of patients. Analysis of a possible relationship between rash and clinical outcome showed that rash developed in all 7 patients with an objective response and in 21 (95%) of 22 patients who had stable disease but in only 15 (54%) of 28 patients who had PD. Thus, rash was not a sufficient condition for tumor response in this study. In addition, patients who had rash had significantly longer survival. The median survival of patients without rash was 1.5 months compared with 8.5 and 19.6 months for patients with a maximum of grade 1 rash and grade 2 or 3 rash, respectively. Furthermore, rash was found to be the most significant predictor of survival.

In a prospective study in which 199 patients with advanced NSCLC were treated with gefitinib (250 mg) upon progression during chemotherapy, Mohamed et al. have shown that rash predicts improved survival[12]. The predictive factors analyzed were sex, rash, diarrhea, histologic type, and PS. Median survival was 10.8 months in patients with rash (any grade) and was significantly longer than that in patients without rash (4.0 months).

On the basis of these earlier studies, we investigated the possible relationship between skin toxicity and survival in patients treated with gefitinib at our hospital. However, we found no significant correlation. This result might be due to our study being retrospective and having only 43 patients, insufficient to yield a statistically significant difference. Furthermore, the response rate was 11.6%, which is lower than the average value in Japanese patients. Furthermore, compared with patients without skin toxicity, patients with skin toxicity were less likely to be female (35.0% versus 26.1%) or nonsmokers (45.0% versus 34.8%) or to have adenocarcinoma (85.0% versus 78.3%) or stage 1 to 3 disease (20.0% versus 13.0%), all of which are associated with a better prognosis. In general, factors predicting a good response to gefitinib are adenocarcinoma and being female, Japanese, or a nonsmoker[2,21]. In our analysis, survival was slightly but not significantly longer in female patients and nonsmokers. Therefore, the results might be attributed to differences in the percentages of characteristics between patients with and without skin toxicity. In future studies significant differences might be achieved by increasing the sample size and matching the characteristics between the

groups.

There is increasing evidence suggesting that the therapeutic efficacy of EGFR inhibitors is related to skin toxicity. In the future, skin toxicity might be a useful surrogate marker for tumor response. Although how the skin toxicity due to EGFR inhibitors is related to survival is unclear, recent studies have explored possible mechanisms. Perea et al. have evaluated the number of CA repeats in the highly polymorphic intron 1 of the EGFR gene[22]. Shorter CA segments were associated with higher expression of the EGFR gene and protein. Patients with short CA segments had a higher frequency of gefitinib-induced rash (61%) than did those with long CA repeats (17%). This finding indicates that patients and tumors with short CA repeat segments in the regulatory intron 1 of the EGFR are more susceptible to the pharmacologic effects of EGFR inhibitors; this finding, therefore, suggests that rash is related to the therapeutic effects of these drugs. Nevertheless, these mechanisms should be clarified to improve the efficacy of EGFR inhibitors in patients with advanced NSCLC.

In summary, we have analyzed patients with advanced NSCLC treated with gefitinib in The Jikei University Hospital. We could find no relationship between survival and skin toxicity. However, analyzing skin toxicity due to gefitinib is worthwhile to determine how it affects the prognosis of NSCLC.

Acknowledgement : We would like to thank Professor Seibu Mochizuki, Chairman of Department of Internal Medicine, The Jikei University School of Medicine, for his valuable guidance and encouragement.

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